REMARKS

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 2 and 19 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the rejection states that the specification does not enable the one to distinguish MS^2 and MS^3 spectra of PGD_2 and PGE_2, and therefore the method recited in claims 2 and 19 can not be performed.

The first paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification "may be enabling even though some experimentation is necessary." *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Applicant respectfully traverses this rejection. The limitation of "distinguishing spectra," upon which the rejection relies, is not present in claim 2 or claim 19. Claim 2 depends from claim 1, which claims a method for performing liquid chromatography-mass spectrometry on a chemical mixture comprising at least two prostaglandins. Claim 2 limits the prostaglandins to PGD_2 and PGE_2. The method does not comprise the step of distinguishing the spectra. The rejection's reference to lack of distinguishing MS^3 and MS^4 spectra, therefore, is immaterial to Claim 2. Similarly, Claim 19 depends from claim 18, which claims a method for performing liquid chromatography-mass spectrometry on a chemical mixture comprising at least two prostaglandins. Claim 19 limits the prostaglandins to PGD_2 and PGE_2. The method does not comprise the step of distinguishing the spectra. The rejection's reference to lack of distinguishing MS^3 and MS^4 spectra, therefore, is immaterial to Claim 19.

Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 11 and 24 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area which applicants regard as their invention with a *reasonable* degree of precision and particularity.

Specifically, the rejection indicates that only two isobaric "isomers," PGD_2 and PGE_2 are mentioned in the specification and it is unclear whether there are other "isomers" which are isobaric. Isobaric ions are simply ions that have the same nominal mass but different exact mass. Determining whether two species are isobaric is therefore a simple matter that would be clear to one skilled in the art. Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 3-5, 11-18 and 20-30 under 35 U.S.C. § 103(a) as being unpatentable over Li, et al., (1999) *PNAS* 96:13381–86, in view of Kamel, et al., 1999, *Anal. Chem.*, 71:5481–92 and Technical Note (2000). The Examiner bears the burden of establishing a prima facie case of obviousness (Section 103). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applicant respectfully traverses this rejection. Li, et al. teach HPLC-MS of F_2-isoprostanes. Li, et al. developed methods to measure individual members of the four structural classes of the F_2-isoprostanes. Li, et al. accomplishes this goal by utilizing homologous internal strandards (page 13381, top of second column). Li, et al. neither teach nor suggest adding a basic liquid (or an acidic liquid) to the sheath flow. Indeed, such an addition is unnecessary for the method of Li, et al.

Kamel, et al., describe the effects of mobile-phase additives in HPLC-MS analysis of nucleoside antiviral agents. Kamel, et al., conclude that mobile phase additives have a significant effect on ESI spectra and conclude that 1% acetic acid, with an apparent pH of 3.1, and 50 mM NH_4OH, with an apparent pH of 10.1, gave the most sensitive results.

The rejection states that it would have been obvious to one of ordinary skill in the art to modify Li's method by adding NH_4OH to the HPLC eluent as disclosed in Kamel, et al. Applicant respectfully traverses this rejection. Li, et al., is concerned with analysis of isoprostanes in human urine. Kamel, et al., is concerned with analysis of nucleoside pharmaceutical agents. Assays for individuals isoprostanes in Li, et al., was accomplished without additives to the mobile phase. In contrast, Kamel, et al. deliberately modified the mobile phase for analysis of nucleoside antiviral agents. Applicant submits that there is no motivation to look to the art of nucleoside pharmaceuticals for guidance in analysis conditions relating to prostaglandin isomers in clinical samples. Additionally, the analysis of Li, et al., is adequate without basic addition to the mobile phase, which further argues against combining the two references. Applicant therefore submits that no *prima facie* case of obviousness has been made with respect to Li, et al., and Kamel, et al., and that the rejection should be withdrawn on this basis alone.

Even if the two references were combined, it is unclear what the result would be. Kamel, et al, indicates that 1% HOAc gave the greatest sensitivity for $[M + H]^+$ ions, which were much larger for the strongly basic purine derivatives than the sensitivities for the $[M + H]^-$ ions. In the case of less basic pyrimidine derivatives, however the sensitivities for the ions were comparable. Kamel, et al., therefore suggests that acidic mobile phases are preferable in some cases. There is no suggestion in Kamel, et al., as to what the proper additive in prostaglandin analysis would be. Furthermore, Li, et al., teaches away from additives in the mobile phase, since additives were not required in the methods of Li, et al. The combination of Li, et al., and Kamel, et al., therefore does not supply the necessary guidance to motivate one of skill in the art to add a basic liquid to the LC eluant in an LC/MS method for prostaglandins.

The addition of the Technical Note does not remedy the deficiencies of Li, et al., and Kamel, et al. Referring to the sheath liquid generally, the Technical Note indicates that acidic OR basic modifer may be added, "*depending on the required ionization.*" (emphasis added). No teaching or guidance is provided on how to determine the "required ionization" for a mixture of

prostaglandins. With regard to the addition of Kamel, et al. or the Technical Note to Li, et al., the teachings are generic, and no indication is given as to which of the parameters or choices is desirable or likely to be successful (e.g., no additive, basic additive, acidic additive). In this situation, the fact that the claimed invention is within the generic teachings of the prior art does not render the claimed invention obvious. Under such circumstances, i.e., where the artisan is invited to simply try each of numerous possible choices, prima facie obviousness is not established. Instead, it is said that the invitation to investigate various possibilities of a genus can, at most, only render the claimed invention "obvious to try," which is not the proper standard under Section 103. *In re O'Farrell*, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). Reconsideration is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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